Metabolic shift in density-dependent stem cell differentiation.

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Public Summary:
BACKGROUND: Vascular progenitor cells (VPCs) derived from embryonic stem cells (ESCs) are a valuable source for cell- and tissue-based therapeutic strategies. During the optimization of endothelial cell (EC) inductions from mouse ESCs using our staged and chemically-defined induction methods, we found that cell seeding density but not VEGF treatment between 10 ng/mL and 40 ng/mL was a significant variable directing ESCs into FLK1(+) VPCs during stage 1 induction. Here, we examine potential contributions from cell-to-cell signaling or cellular metabolism in the production of VPCs from ESCs seeded at different cell densities. METHODS: Using 1D (1)H-NMR spectroscopy, transcriptomic arrays, and flow cytometry, we observed that the density-dependent differentiation of ESCs into FLK1(+) VPCs positively correlated with a shift in metabolism and cellular growth. RESULTS: Specifically, cell differentiation correlated with an earlier plateauing of exhaustive glycolysis, decreased lactate production, lower metabolite consumption, decreased cellular proliferation and an increase in cell size. In contrast, cells seeded at a lower density of 1,000 cells/cm(2) exhibited increased rates of glycolysis, lactate secretion, metabolite utilization, and proliferation over the same induction period. Gene expression analysis indicated that high cell seeding density correlated with up-regulation of several genes including cell adhesion molecules of the notch family (NOTCH1 and NOTCH4) and cadherin family (CDH5) related to vascular development. CONCLUSIONS: These results confirm that a distinct metabolic phenotype correlates with cell differentiation of VPCs.

Scientific Abstract:
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